Dendritic Cell Maturation and Death during *Salmonella* infection

Role of pro-inflammatory cytokines and MyD88

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The thesis is based on the following papers:

I. Malin Sundquist and Mary Jo Wick. TNF-α-dependent and -independent maturation of dendritic cells and recruited $CD11c^{int}CD11b^{+}$ cells during oral *Salmonella* infection.
J. Immunol. 175:3287-98 (2005).

II. Miguel A. Tam*, Malin Sundquist* and Mary Jo Wick. MyD88 and IFN-αβ differentially control maturation of bystander but not *Salmonella*-associated dendritic cells or $CD11c^{int}CD11b^{+}$ cells during infection.
Submitted manuscript. *Authors contributed equally.

III. Malin Sundquist and Mary Jo Wick. *Salmonella* induces apoptosis of $CD8\alpha^{+}$ dendritic cells in the draining lymph node via MyD88-dependent production of TNF.
Manuscript.

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Role of pro-inflammatory cytokines and MyD88

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Abstract

The costimulatory molecules CD80 and CD86 are required for the ability of dendritic cells (DC) to induce both tolerance and immunity. This thesis investigates the control of CD80/CD86 upregulation in vivo on DC during *Salmonella* infection.

After oral *Salmonella* infection, DC in Peyer´s patches (PP), mesenteric lymph nodes (MLN) and spleen upregulated costimulatory molecules almost simultaneously despite differential seeding of these organs with bacteria. Costimulatory molecules were also induced on TNF/iNOS-producing $CD11c^{int}CD11b^{+}$ DC that accumulated in infected organs. The $CD11c^{int}CD11b^{+}$ DC were efficient at bacterial uptake but, in contrast to conventional DC, failed to process and present *Salmonella* Ag on MHC-II.

Using different gene-deficient mice, the pathways controlling CD80/86 upregulation on DC during *Salmonella* infection were dissected. Upregulation of CD80 was strictly dependent on the Toll-like receptor adaptor MyD88, whereas upregulation of CD86 was mediated by both MyD88-dependent and -independent factors. The pro-inflammatory cytokine TNF was identified as one MyD88-dependent factor required for optimal upregulation of CD80/86 in the MLN. In the absence of MyD88, upregulation of CD86 was mediated by type I interferons. However, the contribution of type I interferons to CD86 upregulation in wild type mice is only marginal, since mice lacking the type I interferon receptor (IFN-αβR) showed no major defects in CD80/86 upregulation. Despite the abrogated upregulation of CD80/86 on DC of $TNFR1^{-/-}$, $MyD88^{-/-}$ or $MyD88^{-/-}$IFN-$\alpha\beta R^{-/-}$ mice, DC directly associated with bacteria upregulated costimulatory molecules independently of these factors.

Pro-inflammatory signaling not only upregulated costimulatory molecules on DC during *Salmonella* infection, but also mediated DC death. Thus, MyD88-dependent production of TNF induced DC death in *Salmonella*-infected mice. $CD8\alpha^{+}$ DC were most susceptible to infection-induced cell death as assessed directly ex vivo by Annexin-V and 7AAD staining, whereas recruited $CD11c^{int}CD11b^{+}$ DC were completely resistant.

Thus, the inflammatory environment imprints a distinct pattern of costimulatory molecules on DC, with MyD88-dependent factors controlling the upregulation of CD80. However, MyD88-dependent factors also induce DC death during *Salmonella* infection, which is likely to have a negative impact on anti-bacterial immunity.

Keywords: Dendritic cells, costimulatory molecules, bacterial infection, pro-inflammatory cytokines, Toll-like receptors, Ag presentation, cell death

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